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(71) *Sökande* *AstraZeneca AB, Södertälje SE*
Applicant (s)

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PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

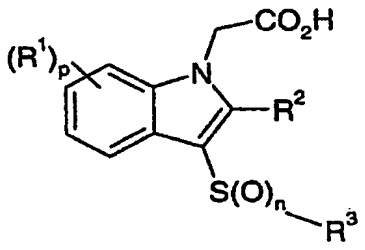
Telefax
+46 8 666 02 86
08-666 02 86

NOVEL COMPOUNDS

The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders, pharmaceutical compositions containing them, and processes for their preparation.

EPA 1 170 594 discloses methods for the identification of compounds useful for the treatment of disease states mediated by prostaglandin D2, a ligand for orphan receptor CRTH2. GB 1356834 discloses a series of compounds said to possess anti-inflammatory, analgesic and antipyretic activity. It has now surprisingly been found that certain indole acetic acids are active at the CRTH2 receptor, and as a consequence are expected to be potentially useful for the treatment of various respiratory diseases, including asthma and COPD.

In a first aspect the invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which:

n represents 1 or 2;

R^1 is halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SO_2R^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^7SO_2R^4$, $NR^7CO_2R^4$, C_2-C_6 alkenyl, C_2-C_6 alkynyl or $C_{1\text{-}6}$alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x is 0,1 or 2;

p is 0 to 4;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, COR^4 or C_{1-7}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x is 0,1 or 2:

R^3 is aryl or heteroaryl group each of which is optionally substituted by one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SO_2R^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^7SO_2R^4$, $NR^7CO_2R^4$, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_{1-6}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x = 0,1 or 2;

R^4 represents hydrogen or C_{1-6}alkyl which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, $-OR^{10}$ and $-NR^{11}R^{12}$.

R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl group, or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, aryl, $-OR^{13}$ and $-NR^{14}R^{15}$, $-CONR^{14}R^{15}$, $-NR^{14}COR^{15}$, $-SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;
or
R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, S, NR^{16}, and itself optionally substituted by C_{1-3} alkyl, halogen;

each of R^7, R^8, R^9 R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6, alkyl, or an aryl group; and

R^{16} is hydrogen, C_{1-4} alkyl, $-COC_1$-C_4 alkyl, $-COYC_1$-C_4alkyl, Y=O or NR^7.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched.

Aryl is phenyl and naphthyl. Heteroaryl is defined as a 5-7 membered aromatic ring or can be 6,6- or 6,5-fused bicyclic each ring containing one or more heteroatoms selected from N, S and O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, isoxazole, pyrrole, isothiazole and azulene, naphthyl, indene, quinoline, isoquinoline, indole, indolizine, benzo[b]furan, benzo[b]thiophene, 1H-indazole,

benzimidazole, benzthiazole, benzoxazole, purine, 4H-quinolizine, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, pteridine, quinolone.

Heterocyclic rings as defined for R^5 and R^6 means saturated heterocycles, examples include morpholine, thiomorpholine, azetidine, imidazolidine, pyrrolidine, piperidine and piperazine.

Preferably R^1 is halogen, nitrile, C_{1-6}alkyl or SO_2R^4 . More preferably R^1 is methyl, nitrile, chloro, SO_2Me, SO_2Et. Preferably p is 1 or 2.

The R^1 groups can be present at any suitable position on the indole ring. preferably the R^1 group(s) is (are) at the 5-position and/or 4-position.

Preferably R^2 is C_{1-6}alkyl, more preferably methyl.

Preferably R^3 is phenyl optionally substituted by halogen, more preferably chloro.

Substituents can be present on any suitable position of an R^3 group, including nitrogen atoms where these are present. More preferably substituents are present at the 4-position.

Preferred compounds of the invention include:
{3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid,
5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid,
6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid,
7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid,
5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid,
5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid,
3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid,
Sodium 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetate,
and pharmaceutically acceptable salts thereof.

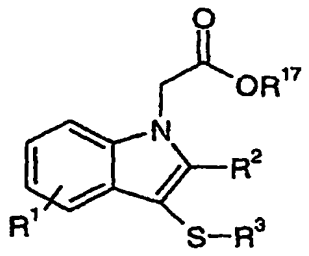
Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

The compound of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably a basic addition salt such as sodium, potassium, calcium, aluminium, lithium, magnesium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethanolamine, ethyldiamine, meglumine, tromethamine or procaine, or an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate. Preferred salts include sodium salts.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups in the starting reagents or intermediate compound may need to be protected by protecting groups. Thus, the preparation of the compound of formula (I) may involve, at an appropriate stage, the removal of one or more protecting groups. The protection and deprotection of functional groups is fully described in 'Protective Groups in Organic Chemistry', edited by J. W. F. McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 3rd edition, T. W. Greene & P. G. M. Wuts, Wiley–Interscience (1999).

Compounds of formula (I) can be prepared by:

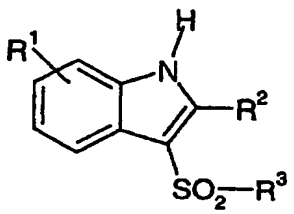
(a) oxidation of a compound of formula (II):



(II)

in which R^{17} is hydrogen or alkyl and R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, or

(b) reaction of a compound of formula (III):



(III)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (IV):

$$R^{18}\text{-}O(CO)CH_2\text{-}L \quad (IV)$$

where R^{18} is an alkyl group and L is a leaving group in the presence of a base, and optionally thereafter (a) or (b) in any order:

- hydrolysing the ester group R^{17} or R^{18} to the corresponding acid
- removing any protecting group
- forming a pharmaceutically acceptable salt.

For process (a) suitable oxidising agents include MCPBA, H_2O_2 or oxone. When R^{17} is alkyl, ethyl or methyl groups are prefered. Where R^{17} is hydrogen compounds of formula (I) are obtained directly by optionally removing of a protecting group and formation of appropriate salts.

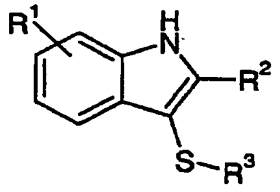
Where R^{17} is alkyl the corresponding ester can be hydrolysed. Hydrolysis of the ester group R^{17} can be carried out using routine procedures, for example by stirring with base, preferably aqueous sodium or lithium hydroxide and optionally removing of protecting group and formation of appropriate salts.

For process (b) the reaction can be carried out in a suitable solvent such as THF using a base such as sodium hydride or the like. Suitable groups R^{18} include C_{1-6} alkyl groups

such as methyl or ethyl. Suitable L is a leaving group such as halo, in particular bromo. Preferably the compound of formula (IV) is ethyl bromoacetate.

Hydrolysis of the ester group R^{18} can be carried out using routine proceduresas described above for R^{17}.

Compounds of formula (III) can be prepared by reaction of a compound of formula (V):



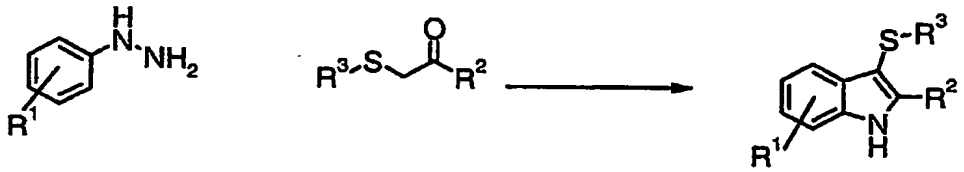
(V)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with an oxidising agent, and optionally thereafter removing any protecting group.

The reaction can be carried out in a suitable solvent such as dichloromethane using an oxidising agent such as MCPBA.

Compounds of formula (II) in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof can be prepared by by reaction of a compound of formula (III) in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof with a compound of formula (IV):

Compounds of formula (V) where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof can be prepared by reacting a compound of formula (VI) with a compound of formula (VII):

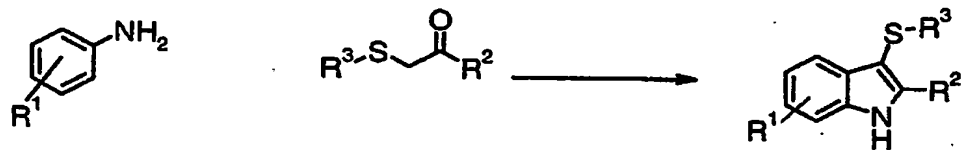


(VI) (VII) (V)

in which R^1, R^2 and R^3 are as defined in formula (I).

Preferably the reaction is carried out in acetic acid with heating.

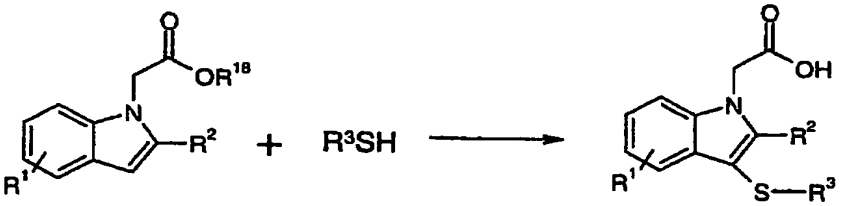
Or, compounds of formula (V) where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, can be prepared by reacting a compound of formula (VIII) with a compound of formula (VII):



(VIII) (VII) (V)

Compounds of formula (VI), ((VII) and (VIII) are commercially available or can be prepared using standard chemistry well known in the art. Where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof.

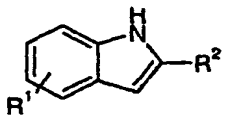
Alterantively compounds of formula (I) can be prepared by reacting compounds of formula (IX) with compounds of formula (X). Where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof.



(IX) (X) (I)

Preferably the reaction is carried out in ethanol with iodine.

Compounds of formula (IX) can be prepared by reaction of compounds of formula (XI) and (IV) as outlined above.



(XI)

Compounds of formula (X) and (XI) are commercially available or can be prepared using standard chemistry well known in the art. Where R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof.

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of CRTh2 receptor activity, and may be used in the treatment (therapeutic or prophylactic) of conditions/diseases in human and non-human animals which are exacerbated or caused by excessive or unregulated production of PGD_2 and its metabolites. Examples of such conditions/diseases include:

(1) **(the respiratory tract)** obstructive airways diseases including: asthma (such as bronchial, allergic, intrinsic, extrinsic and dust asthma particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness)); chronic obstructive pulmonary disease (COPD)(such as irreversible COPD); bronchitis (including eosinophilic bronchitis); acute, allergic, atrophic rhinitis or chronic rhinitis (such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca), rhinitis medicamentosa, membranous rhinitis (including croupous, fibrinous and pseudomembranous rhinitis), scrofoulous rhinitis, seasonal rhinitis (including rhinitis nervosa (hay fever) and vasomotor rhinitis); nasal polyposis; sarcoidosis; farmer's lung and related diseases; fibroid lung; idiopathic interstitial pneumonia; cystic fibrosis; antitussive activity; treatment of chronic cough associated with inflammation or iatrogenic induced ;

(2) **(bone and joints)** arthrides including rheumatic, infectious, autoimmune, seronegative, spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome and systemic sclerosis;

(3) **(skin and eyes)** psoriasis, atopical dermatitis, contact dermatitis, other eczmatous dermitides, seborrhoetic dermatitis, Lichen planus, Pemphigus,

bullous Pemphigus, Epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, chronic skin ulcers, uveitis, Alopecia areatacorneal ulcer and vernal conjunctivitis;

(4) **(gastrointestinal tract)** Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease; food-related allergies which have effects remote from the gut, (such as migraine, rhinitis and eczema);

(5) **(central and peripheral nervous system)** Neurodegenerative diseases and dementia disorders (such as Alzheimer's disease, amyotrophic lateral sclerosis and other motor neuron diseases, Creutzfeldt-Jacob's disease and other prion diseases, HIV encephalopathy (AIDS dementia complex), Huntington's disease, frontotemporal dementia, Lewy body dementia and vascular dementia), polyneuropathies (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy), plexopathies, CNS demyelination (such as multiple sclerosis, acute disseminated/haemorrhagic encephalomyelitis, and subacute sclerosing panencephalitis), neuromuscular disorders (such as myasthenia gravis and Lambert-Eaton syndrome), spinal diorders (such as tropical spastic paraparesis, and stiff-man syndrome), paraneoplastic syndromes (such as cerebellar degeneration and encephalomyelitis), CNS trauma, migraine and stroke.

(6) **(other tissues and systemic disease)** atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus erythematosus; systemic lupus, erythematosus; Hashimoto's thyroiditis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, idiopathic thrombocytopenia pupura; post-operative adhesions, sepsis and ischemic/reperfusion injury in the heart, brain, peripheral limbs and other organs.

(7) **(allograft rejection)** acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease;

(8) Diseases associated with raised levels of PGD_2 or its metabolites.

Thus, the present invention provides a compound of formula (I), or a pharmaceutically-acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

Preferably the compounds of the invention are used to treat diseases in which the chemokine receptor belongs to the CRTh2 receptor subfamily.

Particular conditions which can be treated with the compounds of the invention are asthma, rhinitis and other diseases in which raised levels of PGD_2 or its metabolites. It is preferred that the compounds of the invention are used to treat asthma.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a further aspect, the present invention provides the use of a compound or formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy in combination with drugs used to treat asthma and rhinitis (such as inhaled and oral steroids, inhaled β2-receptor agonists and oral leukotriene receptor antagonists).

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of CRTh2 receptor activity is beneficial.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating diseases mediated by PGD2 or its metabolites wherein the prostanoid binds to its receptor (especially CRTh2) receptor, which comprises administering to a patient a therapeutically effective amount of a

compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

The invention also provides a method of treating an inflammatory disease, especially psoriasis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as herein before defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Preferably the compound of the invention is administered orally.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:
(i) when given, ^{1}H NMR data is quoted in the form of delta values for major diagnostic

protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard;

(ii) mass spectra (MS): generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title and sub-titled compounds of the examples and methods were named using the ACD/name program (version 4.53) from Advanced Chemical Development Inc, Canada;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry, NovaPak or Ex-Terra reverse phase silica column;

(v) solvents were dried with $MgSO_4$ or Na_2SO_4, and

(vi) the following abbreviations are used:

THF = tetrahydrofuran

EtOAc = ethyl acetate

MCPBA = meta-chloroperbenzoic acid.

Example 1

{3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid

(a) 3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indole

To a solution of methylphenylhydrazine (7g) in acetonitrile (100ml) was added 1-[(4-chlorophenyl)thio]acetone (8.84g) and water (10ml). The mixture was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue dissolved in dichloromethane. The solution was washed with sodium hydrogen carbonate, brine, dried (MgSO4) and concentrated *in vacuo*. The residue was recrystallised (methanol) to give the sub-title compound ((6g).

APC+ (M+H) = 288.

(b) 3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indole

3-[(4-chlorophenyl)thio]-2,5-dimethyl-1H-indole (1.85g) was dissolved in dichloromethane (20ml) at °C, to this solution MCPBA (2.85g) was added and stirred for 2 hours. The reaction mixture was then washed with sodium carbonate solution, the organic extracts were dried with $MgSO_4$. Purification by Flash column chromatography (35% EtOAc/ hexane as eluent) gave of the sub-title compound (1.27g).

ES+ (M+H) 320.

(c) ethyl {3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-yl}acetate

The product of example, step a (1.27g) was dissolved in THF (20ml) at °C and NaH (0.115g, 60% dispersion in oil) was added and stirred for 30mins. Ethylbromoacetate (0.66ml) was then added and stirred for 1 hour at room temperature. Ethanol was added to quench the reaction, the solvent was removed and the product washed with water and extracted with EtOAc. Purification by Flash column chromatography (30% EtOAc/hexane as eluent) gave the sub-title compound (0.716g).

ES+ (M+H) 406

(d) {3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid

The product of example 1, step b was then dissolved in ethanol (10ml) and 10% NaOH(aq) (10ml) was added and stirred for 1 hour. The reaction mixture was then acidified with HCl(aq), and extracted with EtOAc. Purification by solid phase extraction using NH_2 sorbent (2g), eluting with acetonitrile followed by 10% acetic acid/acetonitrile, gave the title compound (0.301g).

ES- (M-H) 376.

^{1}H NMR (DMSO) δ 2.42 (3H, s), 2.62 (3H, s), 4.68 (2H, s), 7.01 (1H, dd), 7.29 - 7.33 (1H, m), 7.58 - 7.62 (2H, m), 7.65 - 7.69 (1H, m), 7.87 - 7.93 (2H, m).

Example 2

5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

a) 5-chloro-3-[4(-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole

To a suspension of (4-chlorophenyl)-hydrazine hydrochloride (2g) in acetic acid (30ml) was added 1-[(4-chlorophenyl)thio]-acetone (2.24g), acetonitrile (20ml) and water (10ml). The mixture was strirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue suspended in EtOAc, washed with sodium hydrogen carbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in acetic acid (20ml) and heated to 80°C overnight. The reaction mixture was poured into water, basified using NaOH and the organics extracted into EtOAc. The EtOAc was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by Flash column chromatography (20% EtOAc/hexane as eluent) gave the sub-title compound (2.2g).

^{1}H NMR ($CDCl_3$) δ 8.31 (1H,s), 7.48 (1H, d), 7.26 (2H, m), 7.13 (3H, m), 6.93 (2H, m), 2.51 (3H, s).

b) 5-chloro-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

To a solution of 5-chloro-3-[4(-chlorophenyl)thio]-2-methyl-1*H*-indole (0.2g) in THF (5ml) was added 1M sodium bis(trimethylsilyl)amide solution in THF (0.65ml). The mixture was stirred for 30 minutes before bromo-acetic acid, methyl ester (62µl) was added, the reaction was stirred at room temperature overnight. A further 0.3ml of 1.0M sodium bis(trimethylsilyl)amide solution in THF and 30µl of methyl bromoacetate was added to the mixture and was stirred for a further 3 h. The mixture was then adsorbed onto silica and purified by Flash column chromatography (14% EtOAc/hexane as eluent) to give sub-title compound (0.21g).

^{1}H NMR ($CDCl_3$) d 7.52 (1H, d), 7.27 (1H, d), 7.20-7.10(3H, m), 6.97-6.89 (2H, m), 4.80 (2H, d), 3.79 (3H, d), 2.47(3H, d).

c) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

To a solution of the 5-chloro-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, methyl ester (0.1g) in dichloromethane (5ml) was added MCPBA (121mg). The mixture was stirred at room temperature overnight. The reaction was diluted with dichloromethane (10ml), washed with sodium hydrogen carbonate solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give sub-title compound (0.1g). Used in step (d) without further purification and characterisation.

d) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

To a solution of 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, methyl ester (0.09g) in THF (5ml) was added a 1.25M solution of NaOH(aq) (0.25ml). The reaction was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and the residue dissolved/suspended in water. The pH was adjusted to 2 using dilute HCl(aq) and the solid which precipitated was isolated by filtration, dried under vaccum at 40 °C to give the title compound.

APCI- (M-H) 398

^{1}H NMR (DMSO) δ 7.94 (2H, m), 7.89 (1H, d), 7.67-7.62 (3H, m), 7.29 (1H, m), 5.12 (2H, s), 2.63 (3H, s).

Example 3

6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

a) 6-chloro-3-[4(-chlorophenyl)thio]-2-methyl-1*H*-indole

The subtitle compound was prepared by the method of example 2 part (a) using (3-chlorophenyl)-hydrazine hydrochloride. Product purified using Flash column chromatography (10%EtOAc/hexane as eluent).

^{1}H NMR ($CDCl_3$) δ 8.27 (1H, s) 7.39 (1H, d) 7.34 (1H, d), 7.10 (3H, m), 6.92 (2H, m), 2.50 (3H, s).

b) 6-chloro-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (b) using the product from part (a).

^{1}H NMR ($CDCl_3$) δ 7.43 (1H, d), 7.27 - 7.25 (1H, m), 7.14 - 7.09 (3H, m), 6.92 (2H, dd), 4.85 (2H, s), 3.80 (3H, d), 2.46 (3H, d).

c) 6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (c) using the product from part (b). Used in step (d) without further purification or characterisation.

d) 6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 2 part (d) using the product from part (c).

APCI- (M-H) 398

^{1}H NMR (DMSO) δ 7.94-7.89 (3H, m), 7.80 (1H, d) 7.64 (2H, m), 7.27 (1H, m), 5.13 (2H,s), 2.63 (3H, s).

Example 4

7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

a) 7-chloro-3-[4(-chlorophenyl)thio]-2-methyl-1*H*-indole

The subtitle compound was prepared by the method of example 2 part (a) using (2-chlorophenyl)-hydrazine hydrochloride.

^{1}H NMR ($CDCl_3$) δ 8.48 (1H, s) 7.40 (1H, d), 7.19 (1H, m) 7.13-7.11 (2H, m), 7.06 (1H, t), 6.96-6.92 (2H, m), 2.55 (3H, s).

b) 7-chloro-3-[(4-chlorophenyl)thio]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (b) using the product from part (a).

^{1}H NMR($CDCl_3$) δ 7.44 (1H, d), 7.18 - 7.09 (3H, m), 7.03 (1H, td), 6.92 (2H, dd), 5.37 (2H, d), 3.81 (3H, d), 2.46 (3H, d).

c) 7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 2 part (c) using the product from part (b). Used in step (d) without further purification or characterisation.

d) 7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 2 part (d) using the product from part (c).

APCI- (M-H) 398

^{1}H NMR (DMSO) δ 7.96-7.93 (3H, m), 7.65 (2H, m), 7.30 (1H, m), 7.22 (1H, t) 5.32 (2H, s), 2.70 (3H, s).

Example 5

5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)thio]-2,5-dimethyl-1*H*-indole-4-carbonitrile

A stirred solution of 1-[(4-chlorophenyl)thio]-acetone (6.14g) in dry dichloromethane (150ml) at –78°C was treated with sulphuryl chloride (2.25ml). After 30 min a prepared solution of *N,N,N',N'*-tetramethyl-1,8-naphthalenediamine (6.01g) and 5-amino-2-chloro-benzonitrile (3.89g) in dry dicholoromethane (80ml) was added dropwise over 30 min. The mixture was stirred for a further 2 h, after which triethylamine (4.26ml) was added and the reaction allowed to reach room temperature. The reaction mixture was diluted with dichloromethane (200ml), washed with water, 1N HCl and brine. The organic phase was dried ($MgSO_4$), evaporated *in vacuo*, and the residue purified by flash column chromatography eluting with iso-hexane and ethyl acetate (1:1) to give the sub-title compound (1g), and the regioisomer (600mg) used in example 6 below.

^{1}H NMR $CDCl_3$: δ 12.52 (s,1H), 7.74 (d, 1H), 7.38 (dd, 1H), 7.29 (m, 2H), 6.97 (m, 2H), 3.29 (s, 3H).

b) 3-[(4-chlorophenyl)thio]-4-cyano-2,5-dimethyl-1*H*-indole-1-acetic acid, methyl ester

The sub-title compound was prepared by the method of example 1 part (c) using the product of part (a).
^{1}H NMR $CDCl_3$: δ 7.37 (d, 1H), 7.30 (d, 1H), 7.18 - 7.13 (m, 2H), 7.00 - 6.96 (m, 2H), 4.92 (s, 2H), 3.80 (s, 3H), 2.55 (s, 3H).

(c) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid, methyl ester
The sub-title compound was prepard by the method if example 1 part (b) from the product of part (b).

(d) 5-Chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid
The title compound was prepared by the method of example 1 part (d) using the product of part (c).
^{1}H NMR DMSO : δ 2.81(3H, s), 5.29 (2H, s), 7.62 (1H, s), 7.7 (2H, m), 7.98(2H, m) and 8.08(1H, d).
APCI+(M+H) 422.

Example 6

5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-6-carbonitrile
Obtained from example 5 part a)
^{1}H NMR $CDCl_3$: δ 8.68 (1H, s), 7.69 (1H, s), 7.61 (1H, s), 7.15 (2H, dt), 6.91 (2H. dt), 2.57 (3H, s).

b) 5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid
Prepared by the method of example 2 part d) to give the title compound as a white solid.
^{1}H NMR DMSO: δ 8.42 (1H, s), 7.59 (1H, s), 7.3 (2H, dt), 6.99 (2H, dt), 5.24 (2H, s), 2.46 (3H, s).

M.pt 256-258°C

APCI (M-1) 389

Example 7

3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid, ethyl ester

mCPBA (1.07g) was added to a solution of example 1 part a) (1.79g) in dichloromethane (20 ml) at o C. The reaction mixture was stirred for 1h, after which further mCPBA (53mg) was added and stirred for a further 30 min. The reaction mixture was allowed to reach room temperature and the sub-title compound was obtained as a white solid after filtration (0.68g). Used directly in the next step without further purification.

b) 3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

NaH (0.13g, 60% dispersion in mineral oil) was added to the product from part a) (0.685g) in THF at 0°C. The reaction mixture was stirred for 30 min and then ethyl bromoacetate (0.26 ml) was added and the mixture stirred for 1h. Ethanol was added and then concentrated *in vacuo*. The product was extracted with EtOAc, dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid (761 mg). The solid was dissolved in ethanol (15 ml), NaOH (10% solution, 5 ml) and then the solution stirred overnight. The reaction mixture was acidified (dilute HCl) and extracted with EtOAC. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified with amine resin, eluting with MeCN and then 5% acetic acid in MeCN to give the title compound (60 mg).

^{1}H NMR DMSO: δ 7.61 (4H, s), 7.2-7.25 (1H, m), 6.88-6.91 (1H, m), 6.88-6.86 (1H, m), 4.43 (2H, s), 2.57 (3H, s) and 2.21 (3H, s).

Example 8

3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)thio]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole

Prepared by the method of example 5 part a from 5-(ethylsulfonyl)-2-methoxy-benzenamine.

^{1}H NMR $CDCl_3$: δ 9.00 (1H, s), 7.91 (1H, d), 7.12 (2H, dd), 6.86 (2H, m), 6.73 (1H,d), 4.05 (3H, s), 3.46 (2H,q), 2.46 (3H, s) and 1.16 (3H, t).

b) 3-[(4-chlorophenyl)thio]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid, methyl ester

Prepared by the method of example 5 part b, using the product of sterp a.

^{1}H NMR $CDCl_3$: δ 7.92 (1H, d), 7.13 (2H, dt), 6.85 (2H, dt), 6.73 (1H,d), 5.27 (2H,s),

3.98 (3H, s), 3.79 (3H, s), 3.48 (2H, q), 2.38 (3H,s) and 1.18 (3H, t).

c) 3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid, methyl ester

Prepared by the method of example 5 part c using the product of step b.

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d) 3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid

Prepared by the method of example 5 part d using the product of step c.

^{1}H NMR DMSO: δ 7.79 (1H, d), 7.73 (2H, d), 7.58 (2H, d), 7.04 (1H, d), 5.07 (2H, s), 3.95 (3H, s), 3.58 (2H, q), 2.66 (3H,s) and 1.23 (3H, t).

Example 9

3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 3-[(4-chlorophenyl)thio]-5-cyano-2-methyl-1*H*-indole

To a stirred solution of 4-aminobenzonitrile (5g) in dichloromethane (150ml) cooled to –70°C was added t-butyl hypochlorite (4.6g) dropwise over 5 minutes. The reaction was stirred for 10 minutes before 1-[4-chlorophenyl)thio]-2-propanone (8.49g) was added as a solution in dichloromethane (20ml). After 1 hour triethylamine (5.9ml) was added and the reaction allowed to warm to room temperature. The reaction was diluted with dichloromethane, washed with HCl(aq), brine, dried over MgSO4, and concentrated in vacuo to give a brown solid. Purification by recystallisation from Methanol gave the subtitle compound (7.5g).

^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.84 (s, 1H), 7.44 (dd, 1H), 7.41 (d, 1H), 7.19 – 7.08 (m, 2H), 6.93 (dd, 2H), 2.56 (s, 3H).

b) 3-[(4-chlorophenyl)thio]-5-cyano-2-methyl-1*H*-indole-acetic acid, ethyl ester

The subtitle compound was prepared by the method of example 5 part (b) using the product from part (a) and ethyl bromoacetate. The product was used without further characterisation in part (c).

c) 3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid, methyl ester

mCPBA (128 mg) was added to the product of part (b) (200mg) in dichloromethane (10 ml), and stirred overnight. The solution was washed ($NaHCO_3$), brine, then dried ($MgSO_4$) and concentrated *in vacuo* to give the subtitle compound as a white solid (170 mg).

d) 3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepared by the method of example 5 part (d) using the product of step (c).

^{1}H NMR (DMSO) δ 7.69-7.57 (m, 6H), 7.51 (dd, 1H), 4.85 (dd, 2H) and 2.63 (s, 3H)

Example 10

3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

a) 1*H*-indole-1-acetic acid, 3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid, methyl ester

Th e sub-title compound was prepared by the method of example 5 part (c) using the product of example 9 part (b).

^{1}H NMR (DMSO) δ 8.35 (d, 1H), 8.03 (dt, 2H), 7.82 (d, 1H), 7.71-7.62 (m, 3H), 5.32 (s, 2H), 4.15 (q, 2H), 2.67 (s, 3H) and 1.18 (td, 3H)

b) 1*H*-indole-1-acetic acid, 3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

The title compound was prepeared by the method of example 5 part (d) using the product of step (a)

^{1}H NMR (DMSO) δ 8.35 (d, 1H), 8.05-8.01 (m, 2H), 7.82 (d, 1H), 7.69-7.63 (m, 3H), 5.20 (s, 2H) and 2.67 (s, 3H).

Example 11

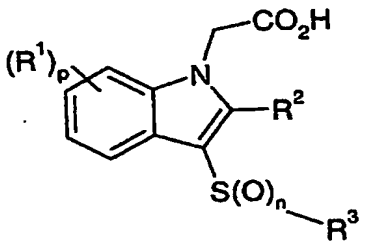
Sodium 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetate

Sodium hydroxide (1M, 4.3 ml) was added to a solution of the product of example 1 part (c) (1.75 g) in THF (60ml). The reaction mixture was stirred overnight and then concentrated *in vacuo*. The residue was recrystallised from water to give the title compound as a white solid.

^{1}H NMR (DMSO) δ 7.89 (dd, 2H), 7.66 (d, 1H), 7.61 (m, 2H), 7.26(d, 1H.), 6.99 (1H, dd), 4.39(s, 2H), 2.59 (s, 3H) and 2.4(s, 3H).

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which:

n represents 1 or 2;

R^1 is halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SO_2R^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^7SO_2R^4$, $NR^7CO_2R^4$, C_2-C_6 alkenyl, C_2-C_6 alkynyl or C_{1-6}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x is 0,1 or 2;

p is 0 to 4;

R^2 is hydrogen, halogen, CN, SO_2R^4 or $CONR^5R^6$, COR^4 or C_{1-7}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x is 0,1 or 2:

R^3 is aryl or heteroaryl group each of which is optionally substituted by one or more substituents independently selected from halogen, CN, nitro, SO_2R^4, OR^4, SR^4, SO_2R^4, $SO_2NR^5R^6$, $CONR^5R^6$, NR^5R^6, $NR^7SO_2R^4$, $NR^7CO_2R^4$, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_{1-6}alkyl, the latter three groups being optionally substituted by one or more substituents independently selected from halogen atoms, $-OR^7$ and $-NR^8R^9$, $S(O)xR^7$ where x = 0,1 or 2;

R^4 represents hydrogen or C_{1-6}alkyl which may be optionally substituted by one or more substituents independently selected from halogen atoms, aryl, $-OR^{10}$ and $-NR^{11}R^{12}$.

R^5 and R^6 independently represent a hydrogen atom, a C_{1-6}alkyl group, or phenyl group the latter two of which may be optionally substituted by one or more substituent groups independently selected from halogen atoms, aryl, $-OR^{13}$ and $-NR^{14}R^{15}$, $-CONR^{14}R^{15}$, $-NR^{14}COR^{15}$,$-SO_2NR^{14}R^{15}$, $NR^{14}SO_2R^{15}$;

or

R^5 and R^6 together with the nitrogen atom to which they are attached can form a 3-8 membered saturated heterocylic ring optionally containing one or more atoms selected from O, S, NR^{16}, and itself optionally substituted by C_{1-3} alkyl, halogen;

each of R^7, R^8, R^9 R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, independently represents a hydrogen atom, C_1-C_6, alkyl, or an aryl group; and

R^{16} is hydrogen, C_{1-4} alkyl, $-COC_1$-C_4 alkyl, $-COYC_1$-C_4alkyl, Y=O or NR^7.

2. A compound according to claim 1 in which n is 2.

3. A compound according to claim 1 or 2 in which R^1 is halogen, nitrile, C_{1-6}alkyl or SO_2R^4.

4. A compound according to any one of claims 1 to 3 in which p is 1 or 2.

5. A compound according to any one of claims 1 to 4 in which R^2 is C_{1-6}alkyl.

6. A compound according to claim 4 in which R^3 is phenyl substituted by halogen..

7. A compound according to claim 1 selected from:
{3-[(4-chlorophenyl)sulfonyl]-2,5-dimethyl-1*H*-indol-1-yl}acetic acid
5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid
6-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid
7-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetic acid
5-chloro-3-[(4-chlorophenyl)sulfonyl]-4-cyano-2-methyl-1*H*-indole-1-acetic acid
5-chloro-3-[(4-chlorophenyl)sulfonyl]-6-cyano-2-methyl-1*H*-indole-1-acetic acid
3-[(4-chlorophenyl)sulfinyl]-2,5-dimethyl-1*H*-indole-1-acetic acid

3-[(4-chlorophenyl)sulfonyl]-4-(ethylsulfonyl)-7-methoxy-2-methyl-1*H*-indole-1-acetic acid

3-[(4-chlorophenyl)sulfinyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

3-[(4-chlorophenyl)sulfonyl]-5-cyano-2-methyl-1*H*-indole-1-acetic acid

Sodium 5-chloro-3-[(4-chlorophenyl)sulfonyl]-2-methyl-1*H*-indole-1-acetate

and pharmaceutically acceptable salts thereof.

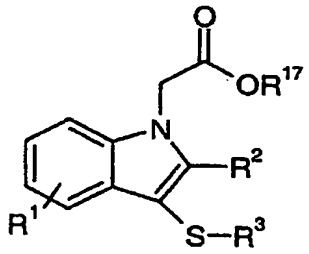
8. A compound of formula (I) according to any one of claims 1 to 7 for use in therapy.

9. A method of treating a disease mediated by prostaglandin D2, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt as defined in claims 1 to 7.

10. A method of treating a respiratory disease, such as asthma and rhinitis, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as defined in claims 1 to 7.

11. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):

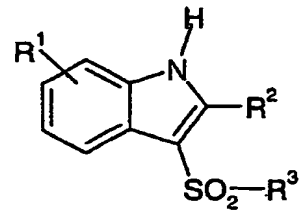
(a) oxidation of a compound of formula (II):



(II)

in which R^{17} is hydrogen or alkyl and R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, or

(c) reaction of a compound of formula (III):



(III)

in which R^1, R^2 and R^3 are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (IV):

$$R^{18}\text{-}O(CO)CH_2\text{-}L \quad (IV)$$

where R^{18} is an alkyl group and L is a leaving group in the presence of a base, and optionally thereafter (a) or (b) in any order:

- hydrolysing the ester group R^{17} or R^{18} to the corresponding acid
- removing any protecting group
- forming a pharmaceutically acceptable salt.

ABSTRACT

The present invention relates to substituted indoles useful as pharmaceutical compounds for treating respiratory disorders.